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Mediterranean diet during pregnancy and childhood respiratory and atopic outcomes: birth cohort study

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Abstract

Evidence for associations between Mediterranean diet (MD) during pregnancy and childhood asthma, allergy and related outcomes is conflicting. Few cohorts have followed children to school age, and none have considered lung function.

In the Avon Longitudinal Study of Parents and Children, we analysed associations between maternal MD score during pregnancy (estimated by a food frequency questionnaire, using an *a priori* defined score adapted to pregnant women; score ranging from 0: low adherence to 7: high adherence) and current doctor-diagnosed asthma, wheeze, eczema, hay fever, atopy, and lung function in 8,907 children at 7-9 years and - for a subset - at 15 years. Interaction between maternal MD and maternal smoking in pregnancy was investigated.

Weak positive associations were found between maternal MD score and childhood maximal mid-expiratory flow (FEF_{25-75}). Higher MD scores were associated with increased z-scores adjusted for age, height and gender (β: 0.06 (0.01, 0.12), P= 0.03). The maternal MD score was not associated with asthma or allergy. The relation between MD score and childhood FEF_{25-75} at 15 years had similar effect estimates but, given the loss to follow up, associations were less precise. Stratifying associations by maternal smoking during pregnancy showed that associations with FEF_{25-75} were only seen in children of never/passive smoking mothers, but no evidence for a statistically significant interaction was found.

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Introduction

Given substantial evidence implicating the prenatal environment in the aetiology of childhood asthma[1], with risk factors including low birth weight[2] and maternal obesity[3], many observational studies have investigated the relation between maternal intake of individual nutrients or foods in pregnancy and the risk of asthma and other allergic outcomes in the offspring. Recent systematic reviews concluded that evidence from these studies was not consistent[4, 5]. Whilst recent randomised controlled trials (RCTs) have suggested that supplementation with vitamin D or fish oil in pregnancy may prevent wheezing in early childhood[6, 7], longer follow-up is needed to determine whether these interventions can prevent childhood asthma. Very few studies have investigated the relation between prenatal nutrition and childhood lung function, although we recently reported weak evidence suggesting that lower prenatal iron and zinc status might be associated with lower lung function in children[8, 9]. The paucity of such studies is perhaps surprising, given that low birth weight has been linked to lower childhood lung function[10], early childhood wheezing is associated with later lung function abnormalities[11], and lung function shortly after birth is associated with childhood asthma[12].

An alternative, but less adopted, approach to investigating the role of maternal diet in pregnancy is to study broader aspects of the diet by defining dietary patterns, which might take into account the inter-correlations and biological interactions that occur between individual foods or nutrients. A Mediterranean diet (MD) is typified by a high intake of vegetables, legumes, fruits and nuts, unrefined cereals, fish and olive oil, a low-to-moderate intake of dairy products, and a low intake of meat and poultry and saturated fats[13]. Given that low birthweight, prematurity and gestational weight gain are risk factors for childhood asthma[2, 3, 14], and low birthweight and premature birth are also risk factors for lower childhood lung function [10, 15], high adherence to a MD in pregnancy might be expected to

protect against asthma and/or impaired lung function in the offspring; in a birth cohort study, low adherence to a Mediterranean-like diet in pregnancy was associated with lower birth weight[16], and a recent RCT found that a MD intervention (with additional extra virgin olive oil and pistachio nuts) reduced the rate of small for gestational age newborns, prematurity and gestational weight gain[17]. It also reduced gestational diabetes[17], which has been associated with an increased risk of atopic eczema and atopy in one observational study[18]. A number of observational studies have investigated whether adherence to a MD in pregnancy might protect against the development of asthma and allergies in the offspring, and a recent systematic review concluded that there was some evidence that higher adherence was associated with a lower risk of wheezing in infancy, but evidence for a lower risk of asthma, wheezing and atopic outcomes later in childhood was lacking [19]. However, only one prospective study followed the children to school age [20] and none examined associations with lung function. As a MD is rich in antioxidants, we might expect any beneficial effects of a MD on childhood outcomes to be greatest amongst offspring of mothers who smoked in pregnancy, since tobacco smoke is a source of oxidative stress [21], and that high adherence to a MD would attenuate the detrimental effects of maternal smoking.

In a large UK population-based birth cohort, we have investigated whether greater adherence to a MD in pregnancy is associated with a reduced risk of asthma and other atopic outcomes and with higher lung function in the offspring at school age.

METHODS

Participants

The Avon Longitudinal Study of Parents and Children (ALSPAC) is a population-based birth cohort that recruited 14,541 predominantly white pregnant women resident in Avon, UK with expected dates of delivery 1st April 1991 to 31st December 1992. These pregnancies resulted in 13,972 singleton or twin children who were alive at one year of age. The cohort has been followed since birth with annual questionnaires and, since age 7 years, with objective measures in annual research clinics. The study protocol has been described previously [22, 23]. Please note that the study website contains details of all the data that are available through a fully searchable data dictionary and variable search tool: http://www.bristol.ac.uk/alspac/researchers/our-data/. Ethics approval was obtained from the ALSPAC Ethics and Law Committee (IRB 00003312) and the Local NHS Research Ethics Committees. Informed consent for the use of data collected via questionnaires and clinics was obtained from participants following the recommendations of the ALSPAC Ethics and Law Committee at the time.

Exposure assessment

Data on maternal diet in pregnancy were collected by a food frequency questionnaire (FFQ) at 32 weeks gestation, covering all the main foods consumed in Britain at the time [24]. This FFQ has been shown to produce mean nutrient intakes for the mothers [24] which were similar to those obtained for women in the British National Diet and Nutritional survey for adults [25, 26].

The questionnaire asked about current weekly frequency of consumption of 43 food groups and food items, with the possibility for respondents to tick one of the following options: never or rarely, once in 2 weeks, 1-3 times a week, 4-7 times a week, more than once a day. More detailed questions were asked about daily consumption of a further eight basic foods (including sugar, coffee and tea). The FFQ was used to estimate total energy intake and daily nutrient intake, by multiplying the daily frequency of consumption of a food by the nutrient content[27] of a standard portion[28] of that food, and summing this for all the foods consumed. Information on portion size was not collected. In order to apply quantitative meaning to the frequency categories, the data were numerically transformed into times per week as follows: i) 0; ii) 0.5; iii) 2; iv) 5.5 and v) 10 times per week. The number of slices of bread consumed each day on average was recorded separately and the amount of milk consumed was estimated from the number of cups of white tea/coffee consumed per day and the frequency of breakfast cereal, milky puddings and milk drinks consumed per week.

A MD score was based on that devised by Chatzi et al [20] for pregnant women, which was adapted from the original MD score by Trichopoulou et al [13]. Chatzi et al included dairy products as beneficial rather than detrimental and did not include alcohol. The score is based on the median weekly intake of six beneficial food groups (vegetables, legumes, fruits/nuts, cereal, fish and dairy) and one detrimental food group (meat) [See online supplement Table S1] for a detailed description of the food groups from the FFQ contributing to each component of the score and median weekly consumption]. Women whose consumption of the beneficial food groups was above the median were assigned a value of 1 and those below were assigned a value of 0. Conversely, for the detrimental food group, consumption below the median was assigned a value of 1 and above the median was assigned a value of 0. The seven food group values were then summed together to obtain a score which

ranged from 0 to 7, with a higher score representing greater adherence to a Mediterranean-style diet.

Outcome assessment

Current doctor-diagnosed asthma was defined in children at 7.5 years (primary outcome) if mothers responded positively to the question 'Has a doctor *ever* actually *said* that your study child has asthma?' and to one or both of the questions 'Has your child had any of the following in the past 12 months: wheezing with whistling; asthma?.

Current wheezing, eczema and hay fever in children at 7.5 years were defined by a positive answer to the question: 'Has your child had any of the following in the past 12 months: wheezing with whistling; eczema; hay fever?'.

Atopy at 7 years was defined as a positive reaction (maximum diameter of any detectable weal) to *D.pteronyssinus*, cat or grass (after subtracting positive saline reactions from histamine and allergen weals, and excluding children unreactive to 1% histamine).

Lung function was measured by spirometry (Vitalograph 2120) at age 8½ years after withholding short-acting bronchodilators for at least 6 hours and long-acting bronchodilators and theophyllines for at least 24 hours. The best of three reproducible flow-volume curves was used to measure forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC) and maximal mid-expiratory flow (FEF_{25-75}), which were further transformed to age, height and gender adjusted standard deviation units[29]. The tests adhered to American Thoracic Society (ATS) criteria for standardisation and reproducibility of flow-volume measurement[30], with the exception of ATS recommendations for duration of expiration[31]; as many children did not fulfil forced expiratory time >6 seconds end of test criteria, a minimal volume change over the final 1 second was used. Lung function was also measured at 15 years.

Potential confounders

We selected potential confounding factors which are known (from existing literature) to be associated with one or more of the outcomes of interest[32]. These included maternal age at delivery, sex of child, multiple pregnancy, season of birth, maternal history of atopic diseases (hay fever, asthma, eczema, allergies, or attacks of wheezing with whistling on the chest or attacks of breathlessness in the past two years), parity, highest educational qualification in UK schools (Certificate of Secondary Education, Vocational, Ordinary level, Advanced level, Degree), housing tenure, financial difficulties, ethnicity, breastfeeding duration, and maternal factors during pregnancy (smoking status, anxiety score [Crown-Crisp Experiential Index][33], paracetamol use, antibiotic use, infections [urinary infection, influenza, rubella, thrush, genital herpes, other], supplement use and total energy intake [kJ/day]). Smoking status was categorised as the maximum exposure during pregnancy (never, passive smoking only, 1-9 cigarettes per day, 10-19 cigarettes per day, ≥20 cigarettes per day).

Statistical analyses

We compared the distributions of child and maternal variables across the maternal MD score categories (≥ 4 versus ≤ 3, as done previously by Chatzi el al [20]) using t-tests for differences in continuous variables and chi-squared tests for differences in categorical variables. Logistic regression, multinomial logistic regression, and linear regression were used to analyse relations between the maternal MD score in pregnancy and binary, categorical and continuous outcomes, respectively. We analysed the maternal MD score first as a binary variable (i.e. ≥ 4 and ≤ 3; [20]) using the lower category as reference, and second as a continuous variable to test for linear trend (i.e. per increasing score-unit effect). For all

regression analyses, two stages of adjustment were used. In Model 1 we adjusted for total energy intake only. In Model 2 we adjusted additionally for all potential confounders listed above.

When evidence for associations persisted, we considered other factors which could be considered either as potential confounders or potential mediators of associations between maternal MD in pregnancy and childhood outcomes, namely, prematurity [14, 15, 17], impaired fetal growth[2, 10, 16, 17], maternal obesity and weight gain [3, 17] and offspring obesity[34, 35]. We therefore adjusted additionally for maternal pre-pregnancy body mass index (BMI) (self-reported), gestational age at delivery, birth weight, maternal weight gain during pregnancy (all abstracted from obstetric records) and child's BMI at 7 (based on measured height and weight at clinic) (See online Figure S1 in the online supplement showing a directed acyclic graph). As a MD is rich in antioxidants, we might expect any beneficial effects on childhood outcomes to be greatest amongst offspring of mothers who smoked in pregnancy, since tobacco smoke is a source of oxidative stress[21]. We therefore stratified the dietary analyses by maternal smoking history (dichotomised) to explore potential effect modification by smoking and tested for interaction. We also explored whether the association between maternal smoking in pregnancy and FEF_{25-75}, previously reported in ALSPAC [36], was modified by MD score (dichotomised).

As sensitivity analyses, we repeated analyses after exclusion of mothers with implausible energy intakes (<2,500 or >25,000 kJ/day[37]). To correct for potential loss to follow-up bias, we used inverse probability weighting and assigned to each woman a weight that is the inverse of the probability of her selection for given values of covariates (see further details online) [38]. All statistical analyses were carried out using Stata version 12.1 (StataCorp LP, USA).

RESULTS

Of the 13,972 singleton or twin children alive at one year of age, information on maternal diet was available for 11,993, of whom there was information on at least one of the outcomes of interest for 8,907 (online Figure S2). Characteristics of the 8,907 mother-child pairs who were included in the analyses, and those of the 3,086 mother-child pairs with information on maternal diet who were excluded because of incomplete outcome data, are compared in online Table S2.

Women in the higher category of MD score during pregnancy were older and more educated than women in the lower category. They were more likely to give birth in winter or spring, to breastfeed for 3 months or longer, to be better educated, to have an owned/mortgaged house and to use supplements during pregnancy. They were less likely to have financial difficulties, to have a high anxiety score, to smoke or to use paracetamol during pregnancy. They also had a lower pre-pregnancy BMI, higher total energy intake, and gained more weight during pregnancy. Their offspring were more likely to have weighed more at birth and less likely to have a high BMI at 7 (Table 1).

After controlling for confounders, maternal MD score (whether analysed as a binary or continuous variable), was not associated with asthma, wheeze, eczema, hayfever or atopy (Table 2). When we analysed the associations between the maternal MD score and childhood lung function at 8-9 years after controlling for total energy intake only, strong evidence was found for positive associations with childhood FEV_1 and FEF_{25-75}. These associations slightly weakened after further adjustment for potential confounders, but evidence for a positive association with childhood FEF_{25-75} persisted when comparing higher versus lower maternal MD score (difference in age, height and gender adjusted standard deviation units: 0.06 (95% CI: 0.01, 0.12), P-value: 0.03) (Table 3). When we analysed the relation between MD score and childhood lung function at 15 years, the per-unit increase effect estimates for FEF_{25-75}

were similar to those observed at 8 years (online Table S3); however given the smaller sample size, associations were no longer conventionally significant,

Additional separate adjustment for maternal pre-pregnancy BMI, gestational age at delivery, birth weight, maternal weight gain during pregnancy and child's BMI at 7 did not alter the main findings (data not shown) and therefore no further formal mediation analysis was conducted. Excluding mothers with implausible energy intakes did not alter the main findings, nor did the inverse probability weighting analysis (data not shown).

When we stratified the analyses of MD and lung function by maternal smoking in pregnancy, maternal MD was positively associated with childhood FEF_{25-75} amongst non/passive smokers, but not amongst active smokers, but no evidence for a statistically significant interaction was found (Table 4). Conversely, when we stratified the negative association between maternal smoking in pregnancy and FEF_{25-75} by MD score (dichotomised), there was no evidence of attenuation of the association by higher adherence to a MD (data not shown).

Discussion

This is the largest observational study to investigate the relation between MD in pregnancy and childhood respiratory and allergic outcomes. A limitation of the evidence to date is that many studies have assessed maternal diet retrospectively or have only investigated outcomes in infancy. Of two cohort studies which assessed MD during pregnancy and outcomes beyond infancy, one from Spain (n=460) reported significant negative associations with wheeze and atopy at 6.5 years [20], another larger study from the US (n=1,376) found no association with asthma, wheeze or atopy at 3 years [39]. Given the much larger size of ALSPAC, and our null findings for childhood asthma, wheeze and allergic outcomes, we would argue that the weight of current prospective evidence suggests that adherence to a MD in pregnancy is unlikely to reduce the risk of these conditions at school age. However, we found weak evidence that a higher MD score during pregnancy was associated with higher FEF_{25-75} in the offspring, after controlling for potential confounders. Previous studies have not investigated the relation between MD in pregnancy and childhood lung function; to the best of our knowledge this is a novel finding.

Mechanisms

If the association between MD in pregnancy and lung function in the offspring is causal, one plausible explanation is that it is mediated through the high antioxidant content of the fruit, vegetables and cereals in a MD [19]. If this were the case we would have expected to see an interaction between maternal MD score in pregnancy and maternal smoking on childhood FEF_{25-75}. To our knowledge, this has not been investigated before. We hypothesized *a priori* that a higher MD score in pregnancy might be particularly beneficial if the fetus was exposed to tobacco smoke, by protecting the developing lung from potentially damaging oxidative stress[21]. In fact, there was no association between a MD in pregnancy and lung function amongst active smokers. On the contrary, an association was only seen amongst mothers who

had not actively smoked in pregnancy. An alternative, *post hoc,* hypothesis could be that benefits are only seen above a certain threshold of adherence to a MD, and we have confirmed that mothers who did not actively smoke in pregnancy had a higher MD score than those who did. We also found no evidence that the detrimental effects of maternal smoking on childhood FEF_{25-75} were attenuated by higher adherence to a MD. Apart from its antioxidant properties, a MD may also have anti-inflammatory effects [40]. Part of this effect may reflect the anti-inflammatory properties of omega-3 PUFAs in oily fish. We speculate that this might partly explain the association between a MD in pregnancy and offspring lung function that we observed; a recent trial reported that fish oil-derived omega-3 fatty acid supplementation in pregnancy reduced the risk of early childhood wheezing in the offspring [7], and early childhood wheezing is associated with later reductions in lung function [11]. We found no evidence to suggest that the association between maternal MD score and childhood FEF_{25-75} was mediated by maternal BMI, gestational weight gain or child's BMI, nor by prematurity or low birthweight.

Strengths and limitations

Strengths of the ALSPAC birth cohort include its population-based prospective design, rich information on numerous potential confounders, detailed phenotypic outcome measurements, and its size, which gave us greater statistical power than the previous birth cohort study that has investigated this research question in offspring of school age[20].

The MD score has been developed in Mediterranean countries and is based on population-specific median values. Thus it may not be adapted to non-Mediterranean countries such as the UK, in which median intakes of some specific foods may be lower, and potential beneficial effects might be missed. However, the fact that similar results were observed when the MD score was studied as a binary (above versus below median) or as a

continuous variable makes this possibility less likely. A previous study of maternal dietary patterns in pregnancy in relation to childhood respiratory outcomes has been conducted in ALSPAC, using principal component analysis (PCA) to derive dietary patterns [41]. That study showed that dietary patterns in pregnancy, including a 'health conscious' pattern (which had some similarities to a MD), did not predict asthma and related outcomes in the offspring after controlling for confounders. However, data-driven methods such as PCA are population-specific, and using *a priori* approaches such as the MD score is more relevant in terms of public health. Other *a priori* approaches such as the Alternate Healthy Eating Index (AHEI) score, which is based on international guidelines and has been adapted for pregnant women (AHEI-P) [42], may be more adapted to non-Mediterranean populations; however given the lack of information on some specific AHEI-P food/nutrient items in ALSPAC's FFQ (eg. *trans*-fat), it was not applicable in ALSPAC pregnant women.

Although the FFQ that we used had not been formally calibrated against other instruments such as diet diaries, it was based on the one used by Yarnell et al which has been validated against weighed dietary records [43], and modified in the light of a more recent weighed dietary survey [24]. Whilst there might have been some misclassification of dietary exposures (eg. bread consumption was assessed differently compared to other food groups, and thus may have been overestimated), this is likely to have been non-differential with respect to the outcomes of interest, and would be expected to bias effect estimates towards the null; in other words, the magnitude of associations may have been underestimated, and small or modest effects may have been missed. The possibility that the association between MD in pregnancy and offspring lung function might be explained by uncontrolled or residual confounding cannot be ruled out, especially given that the MD score is highly correlated with social and lifestyle factors. However, we think that this is unlikely, as we controlled for numerous potential confounders in the analyses. As with any longitudinal study, we cannot rule out the

possibility that exclusion of mother-child pairs without complete information might have biased our findings. However, it could be argued that, for our results to be totally spurious for the MD score and childhood lung function in those included in our analysis (and for the associations to be truly null in the population as a whole), associations in the excluded mother-child pairs would have to be at least of equal magnitude in the opposite direction, which seems unlikely. Furthermore, loss to follow-up bias has been shown to only slightly modify associations in longitudinal studies, including in ALSPAC [44], and the results of our inverse probability weighting analysis confirmed that loss to follow-up is unlikely to have biased our results. In view of the multiple analyses carried out, we cannot exclude the possibility that the associations between MD in pregnancy and offspring lung function occurred by chance; hence they should be interpreted with caution and require replication in another birth cohort study. Given the *a priori* nature of the general hypothesis being tested (ie. beneficial effect of a MD), and the fact that some outcomes of interest were highly correlated, it did not seem appropriate to correct for multiple testing.

Conclusions

We found weak evidence that greater adherence to a MD in pregnancy is associated with higher small airway function in the offspring. Further studies in school-aged children are needed to confirm these results.

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Authors' contributions:

AB, KN and SS conceived the study and drafted the manuscript. All authors were involved in the analysis strategy, KN gave advice on the dietary data, and AB performed the statistical analyses. AJH was responsible for all clinical respiratory and allergy data collection. All authors participated in the interpretation of the findings, reviewed the manuscript and revised it critically before submission. All authors have seen and approved the final version of the manuscript.

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Table 1. Characteristics of mothers and offspring who had information on at least one of the outcomes of interest (wheeze, asthma, atopy, eczema, hayfever, total IgE, lung function) by maternal Mediterranean diet score in pregnancy (n=8,907)

Mother and offspring characteristics	Mediterranean diet score		*P**
	0-3 (n=3,475)	4-7 (n=5,432)	
Mother's age (years), m (sd)	28.1 (4.7)	29.4 (4.5)	<.001
Parity, %			
0	45.2	45.7	
1	36.3	35.7	0.83
≥2	18.5	18.6	
Sex of child, %			
Male	50.0	51.9	0.08
Female	50.0	48.1	
Multiple pregnancy, %			
Singleton	97.5	97.6	0.66
Twin	2.5	2.4	
Season of birth, %			
Winter	15.9	16.3	
Spring	25.1	28.3	
Summer	30.0	30.1	<.001
Autumn	29.0	25.4	
Breastfeeding duration, %			
Never	28.6	16.5	
<3 months	35.3	29.2	<.001
3-6 months	12.2	14.8	
≥6 months	23.9	39.5	
Mother's educational level, %			
Certificate of Secondary Education	21.3	11.6	
Vocational	11.7	7.3	
Ordinary level	38.7	33.4	<.001
Advanced level	19.4	28.7	
Degree	8.9	19.0	
Maternal ethnicity, %			
White	98.0	98.3	0.38
Non-white	2.0	1.7	
Housing tenure, %			
Owned/mortgaged	78.2	87.3	
Council rented	14.2	6.4	<.001
Non-council rented	7.6	6.3	
Financial difficulties, %			

Yes	19.8	15.4	<.001
Maternal history of atopic diseases, %			
Yes	69.1	67.9	0.24
Maternal anxiety score in pregnancy, %			
0-9	18.4	23.1	
10-14	25.0	26.2	<.001
15-20	25.7	26.1	
≥20	31.0	24.7	
Maximum maternal tobacco exposure, %			
None	21.5	29.7	
Passive only	44.7	46.7	
1-9 cig/day	7.9	7.9	<.001
10-19 cig/day	14.1	9.6	
20+ cig/day	11.8	6.0	
Maternal paracetamol use during pregnancy, %			
Yes	64.6	61.0	0.001
Maternal antibiotic use during pregnancy, %			
Yes	16.0	16.2	0.81
Maternal dietary supplement use during pregnancy, %	54.4	58.4	<.001
Yes			
Maternal infections in pregnancy, %			
Yes	45.1	46.2	0.33
Total energy intake (kcal/day), m (sd)	1600 (451)	1826 (459)	<.001
Maternal pre-pregnancy BMI, %			
<18.50 kg/m²	4.1	4.4	
18.50-24.99 kg/m²	71.4	77.8	<.001
25.00-29.99 kg/m²	17.4	13.7	
≥30.00 kg/m²	7.1	4.1	
Birth weight, %			
<2500 g	5.0	3.8	
2500-2999 g	14.6	13.3	
3000-3499 g	35.8	35.3	0.006
3500-3999 g	31.9	34.0	
≥4000 g	12.7	13.7	
Gestational age (weeks), m (sd)	39.4 (1.8)	39.5 (1.8)	0.13
Child's BMI at 7, %			
<15.00 kg/m²	28.0	28.1	
15.00-17.49 kg/m²	51.7	53.0	0.01
17.50-20.49 kg/m²	15.2	15.2	
≥20.50 kg/m²	5.2	3.6	

Maternal weight gain during pregnancy, %			
Quartile 1	27.8	23.7	
Quartile 2	23.8	25.5	0.001
Quartile 3	25.1	25.7	
Quartile 4	23.4	25.1	

*Chi-squared tests were used for categorical variables, and t-tests were used for continuous variables.

Table 2. Associations between maternal Mediterranean diet score during pregnancy and asthma, wheeze, eczema, hay fever and atopy in the offspring (n=8, 629)

	Mediterranean diet score			
	4-7 versus 0-3	*P*-value	**Per unit increase**	*P*-trend
Asthma (n=7,634)				
OR[a] (95% CI)	0.94 (0.81, 1.09)	0.41	0.97 (0.92, 1.01)	0.15
OR[b] (95% CI)	1.03 (0.88, 1.20)	0.71	1.00 (0.95, 1.05)	0.93
Wheeze (n=7,719)				
OR[a] (95% CI)	1.02 (0.88, 1.19)	0.80	1.01 (0.96, 1.06)	0.84
OR[b] (95% CI)	1.04 (0.89, 1.22)	0.62	1.01 (0.96, 1.07)	0.63
Eczema (n=7,705)				
OR[a] (95% CI)	1.13 (0.99, 1.29)	0.07	1.03 (0.99, 1.07)	0.18
OR[b] (95% CI)	1.10 (0.96, 1.26)	0.18	1.01 (0.97, 1.06)	0.55
Hay fever (n=7,685)				
OR[a] (95% CI)	1.00 (0.85, 1.18)	0.99	1.01 (0.96, 1.07)	0.72
OR[b] (95% CI)	0.97 (0.81, 1.15)	0.69	1.00 (0.94, 1.06)	0.97
Atopy (n=6,078)				
OR[a] (95% CI)	1.03 (0.90, 1.17)	0.66	1.03 (0.98, 1.07)	0.23
OR[b] (95% CI)	0.94 (0.82, 1.07)	0.34	0.99 (0.95, 1.04)	0.81

OR: Odds ratio

[a] Controlling for energy intake

[b] Controlling for energy intake, smoking, infections, supplements, antibiotics and paracetamol use during pregnancy; maternal educational level, housing tenure, financial difficulties, ethnicity, age, parity, history of atopic diseases, anxiety; sex of child, season of birth, multiple pregnancy, breastfeeding duration

Table 3. Associations between maternal Mediterranean diet score during pregnancy (binary and continuous) and FEV_1, FVC and FEF_{25-75} in the offspring (n=6,120)

	Mediterranean diet score			
	4-7 versus 0-3	*P*-value	**Per unit increase**	*P*-trend
FEV_1 (n=6,026)				
β [a] (95% CI)	0.07 (0.01, 0.12)	0.01	0.03 (0.01, 0.04)	0.005
β [b] (95% CI)	0.05 (-0.01, 0.10)	0.11	0.02 (0.00, 0.04)	0.06
FVC (n=6,120)				
β [a] (95% CI)	0.03 (-0.03, 0.08)	0.36	0.01 (0.00, 0.03)	0.12
β [b] (95% CI)	0.01 (-0.05, 0.06)	0.78	0.01 (-0.01, 0.03)	0.38
FEF_{25-75} (n=6,120)				
β [a] (95% CI)	0.08 (0.02, 0.13)	0.005	0.02 (0.01, 0.04)	0.01
β [b] (95% CI)	0.06 (0.01, 0.12)	0.03	0.02 (0.00, 0.04)	0.06

GMR: geometric mean ratio; β: difference in age, height and gender adjusted standard deviation units

[a] Controlling for energy intake

[b] Controlling for energy intake, smoking, infections, supplements, antibiotics and paracetamol use during pregnancy; maternal educational level, housing tenure, financial difficulties, ethnicity, age, parity, maternal history of atopic diseases, anxiety score; sex of child, season of birth, multiple pregnancy, breastfeeding duration

Table 4. Associations between maternal Mediterranean diet score during pregnancy and childhood lung function stratified by maternal smoking during pregnancy (n=6,115)

	Mediterranean diet score, β* (95% CI)			
	4-7 versus 0-3	*P*-value	**Per unit increase**	*P*-trend
FEV_1				
Non/passive smokers (n=4,479)	0.05 (-0.02, 0.11)	0.15	0.02 (0.00, 0.04)	0.10
Active smokers (n=1,542)	0.04 (-0.07, 0.15)	0.45	0.02 (-0.02, 0.06)	0.29
P interaction [a]	0.81		0.96	
FVC				
Non/passive smokers (n=4,558)	0.01 (-0.05, 0.08)	0.71	0.01 (-0.02, 0.03)	0.59
Active smokers (n=1,557)	0.01 (-0.09, 0.12)	0.80	0.02 (-0.02, 0.05)	0.33
P interaction [a]	0.69		0.90	
FEF_{25-75}				
Non/passive smokers (n=4,558)	0.07 (0.00, 0.13)	0.04	0.02 (0.00, 0.04)	0.05
Active smokers (n=1,557)	0.04 (-0.07, 0.15)	0.44	0.01 (-0.03, 0.04)	0.70
P interaction [a]	0.86		0.68	

β: difference in age, height and gender adjusted standard deviation units

* Controlling for energy intake, infections, supplements, antibiotics and paracetamol use during pregnancy; maternal educational level, housing tenure, financial difficulties, ethnicity, age, parity, maternal history of atopic diseases, anxiety score; sex of child, season of birth, multiple pregnancy, breastfeeding duration

[a] treating smoking as a binary variable and the Mediterranean diet score as either a binary or continuous variable

June 19th 2019

Dear Professor Kuehni,

Please find enclosed our paper entitled "Mediterranean diet during pregnancy and childhood respiratory and atopic outcomes: birth cohort study".

Evidence for associations between a maternal Mediterranean diet (MD) during pregnancy and childhood asthma, allergy and related outcomes is conflicting, with few longitudinal studies following children to school age, and none have considered lung function. We have investigated the associations between maternal MD in pregnancy and childhood atopic and respiratory outcomes at school age, in the large UK population-based birth cohort ALSPAC (The Avon Longitudinal Study of Parents and Children). We have found evidence suggesting adherence to a MD during pregnancy may be associated with increased small airway function in childhood but, contrary to some previous smaller studies, we found no evidence for a reduced risk of asthma or allergy. Given the size of our study, we believe it represents an important contribution to the literature on maternal diet in pregnancy and childhood atopy and respiratory health. We hope that this paper will be of interest to the *ERJ* readership.

This manuscript is not published or submitted for publication elsewhere and all the authors have read it, agreed that this work is ready for submission and have accepted the responsibility for its content.

Looking forward to hearing your decision.

With kind regards,

Annabelle Bédard

e-mail: a.bedard@qmul.ac.uk

Online data supplement

Mediterranean diet during pregnancy and childhood respiratory and atopic outcomes: birth cohort study

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Supplementary methods

Inverse probability weighting

Inverse probability weighting has been proposed as a way to correct for selection bias [1]. By assigning to each subject a weight that is the inverse of the probability of his/her selection based on a given set of covariates and exposure, inverse probability weighting creates a pseudo-population in which effect measures are not affected by selection bias (provided that the outcome in the uncensored subjects truly represents the outcome in the censored subjects for the same values of covariates and exposure). We used this approach by estimating for each woman, the probability of her selection for given values of covariates (ie. the characteristics for which differences between excluded and included women were found to be statistically significant, including the exposure – see online Table 1) and assigning her a weight that is the inverse of that probability.

References

1. Hernán MA, Hernandez-Diaz S, Robins JM. A structural approach to selection bias. *Epidemiology* 2004; 15: 615–625.

Online Table S1: Food groups from the FFQ contributing to the Mediterranean score calculation and estimated median weekly consumption.

MD Component	Food groups from FFQ[1]	Median weekly consumption	% of mother scoring 1
Vegetables	Peas/sweetcorn Green leafy vegetables Other green vegetables Carrots Other root vegetables Salad	10.5 times	50.9%
Legumes	Baked beans Pulses Bean curd Tahini Soya meat	2.0 times	60.2%
Fruit and nuts	Fresh fruit Nuts	5.5 times	66.4%
Cereal	Rice Oat cereals Bran cereals Other cereals Bread[2]	22 times	51.0%
Fish	White fish Shell fish Oily fish	1.5 times	53.1%
Meat	Red Meat Sausages/burgers Pies/pasties Poultry Offal	5 times	49.2%
Dairy	Milk[3]	6553.3g	50.1%

[1] frequency of consumption of these food groups were summed together to obtain an overall 'weekly consumption' for each component

[2] Bread consumption was recorded as the number of slices consumed per day. This was multiplied by 7, to obtain weekly consumption.

[3] Milk consumption estimated based on responses to questions asking the mother about how often she consumed milk as a drink on it's own, milky drinks and milky puddings. This data was combined with milk consumption through tea, coffee and cereal. As these could not all

be readily converted into a frequency of consumption we estimated actual consumption in grams.

Online Table S2. Characteristics of mothers and offspring who were included in analyses and those who were excluded (n=11,993)

	Included (n=8,907)	Excluded (n=3,086)	*P*
Maternal Mediterranean diet score, m (sd)	3.9 (1.5)	3.5 (1.5)	< .001
Mother's age (years), m (sd)	28.9 (4.6)	26.5 (5.1)	< .001
Parity, %			
0	45.5	43.1	
1	36.0	34.3	< .001
≥2	18.5	22.7	
Sex of child, %			
Male	51.2	52.1	0.38
Female	48.8	47.9	
Multiple pregnancy, %			
Singleton	97.6	97.2	0.22
Twin	2.4	2.8	
Season of birth, %			
Winter	16.1	15.9	
Spring	27.1	26.7	0.56
Summer	30.1	31.4	
Autumn	26.8	26.1	
Breastfeeding duration, %			
Never	21.2	35.7	
<3 months	31.6	32.9	< .001
3-6 months	13.8	10.4	
≥6 months	33.5	20.9	
Mother's educational level, %			
Certificate of Secondary Education	15.4	32.8	
Vocational	9.0	12.3	< .001
Ordinary level	35.5	32.4	
Advanced level	25.1	15.7	
Degree	15.1	6.9	
Maternal ethnicity, %			
White	98.2	95.5	< .001
Non-white	1.8	4.5	
Housing tenure, %			
Owned/mortgaged	83.7	62.3	
Council rented	9.4	24.1	< .001
Non-council rented	6.8	13.6	
Financial difficulties, %			
Yes	17.1	22.9	< .001
Maternal history of atopic diseases, %			

Yes	68.4	68.9	0.63
Maternal anxiety score in pregnancy, %			
0-9	21.2	16.9	
10-14	25.7	21.4	< .001
15-20	25.9	24.6	
≥20	27.2	37.2	
Maximum maternal tobacco exposure, %			
None	26.5	17.2	
Passive only	45.9	36.0	< .001
1-9 cig/day	7.9	9.6	
10-19 cig/day	11.4	20.0	
20+ cig/day	8.3	17.2	
Maternal paracetamol use during pregnancy, %	62.4	64.9	0.01
Yes			
Maternal antibiotic use during pregnancy, %			
Yes	16.1	14.6	0.04
Maternal supplement use during pregnancy, %			
Yes	56.8	58.9	0.05
Maternal infections in pregnancy, %			
Yes	45.8	46.9	0.28
Total energy intake (kJ/day), m (sd)	7271 (1962)	7174 (2147)	0.02
Maternal pre-pregnancy BMI, %			
<18.50 kg/m²	4.3	6.4	
18.50-24.99 kg/m²	75.3	72.8	< .001
25.00-29.99 kg/m²	15.1	15.0	
≥30.00 kg/m²	5.3	5.9	
Birth weight, %			
<2500 g	4.3	5.6	
2500-2999 g	13.8	15.1	0.001
3000-3499 g	35.5	36.6	
3500-3999 g	33.2	30.8	
≥4000 g	13.3	11.9	
Gestational age (weeks), m (sd)	39.5 (1.8)	39.4 (1.8)	0.06
Child's BMI at 7, %			
<15.00 kg/m²	28.1	32.7	
15.00-17.49 kg/m²	52.5	41.8	0.38
17.50-20.49 kg/m²	15.2	18.2	
≥20.50 kg/m²	4.2	7.3	
Maternal weight gain during pregnancy, %			

Quartile 1	25.3	28.2	
Quartile 2	24.8	24.4	< .001
Quartile 3	25.5	22.1	
Quartile 4	24.4	25.3	

Online Table S3. Associations between maternal Mediterranean diet score during pregnancy (binary and continuous) and lung function at 15 years (n=3,549)

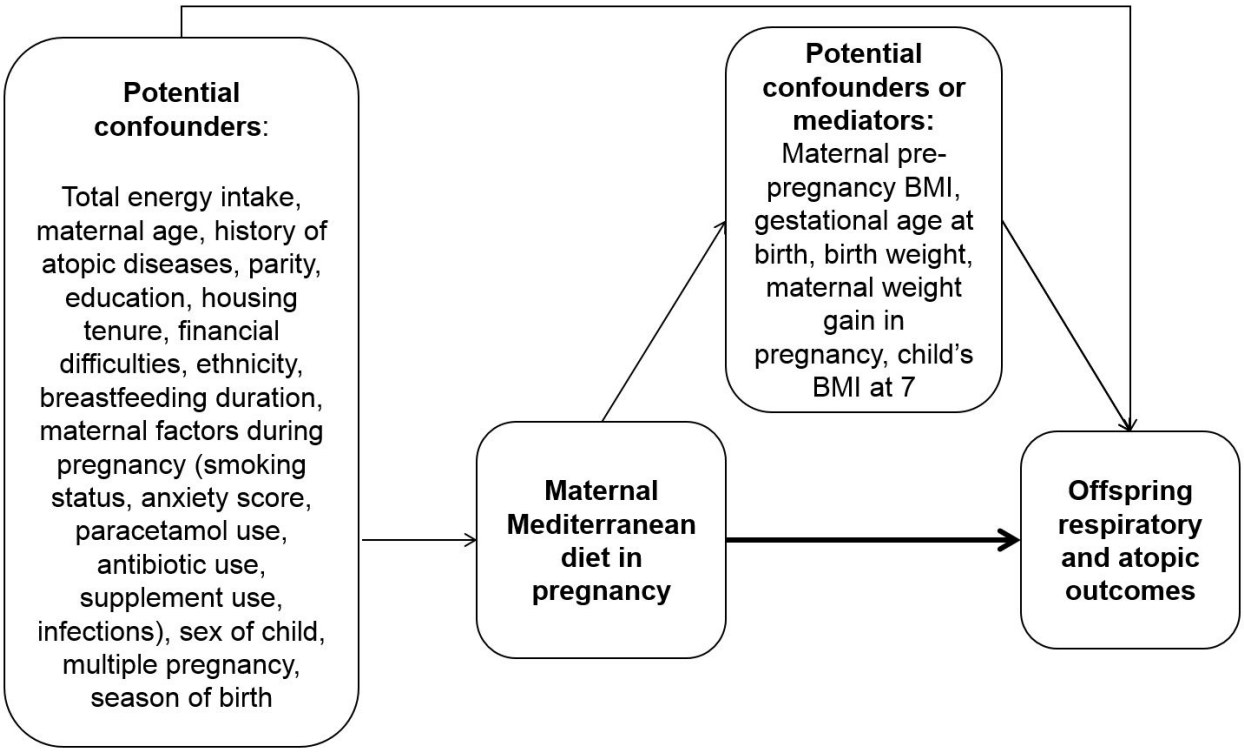
	Mediterranean diet score			
	4-7 versus 0-3	*P*-value	**Per unit increase**	*P*-trend
FEV_1 (n=3,404)				
β [a] (95% CI)	0.04 (-0.03, 0.11)	0.31	0.01 (-0.01, 0.04)	0.33
β [b] (95% CI)	0.04 (-0.03, 0.12)	0.27	0.02 (-0.01, 0.04)	0.23
FVC (n=3,549)				
β [a] (95% CI)	0.02 (-0.06, 0.09)	0.67	0.01 (-0.02, 0.03)	0.51
β [b] (95% CI)	0.02 (-0.05, 0.10)	0.54	0.01 (-0.01, 0.04)	0.32
FEF_{25-75} (n=3,549)				
β [a] (95% CI)	0.05 (-0.02, 0.12)	0.20	0.02 (0.00, 0.05)	0.06
β [b] (95% CI)	0.04 (-0.04, 0.11)	0.32	0.02 (0.00, 0.04)	0.10

β: difference in age, height and gender adjusted standard deviation units

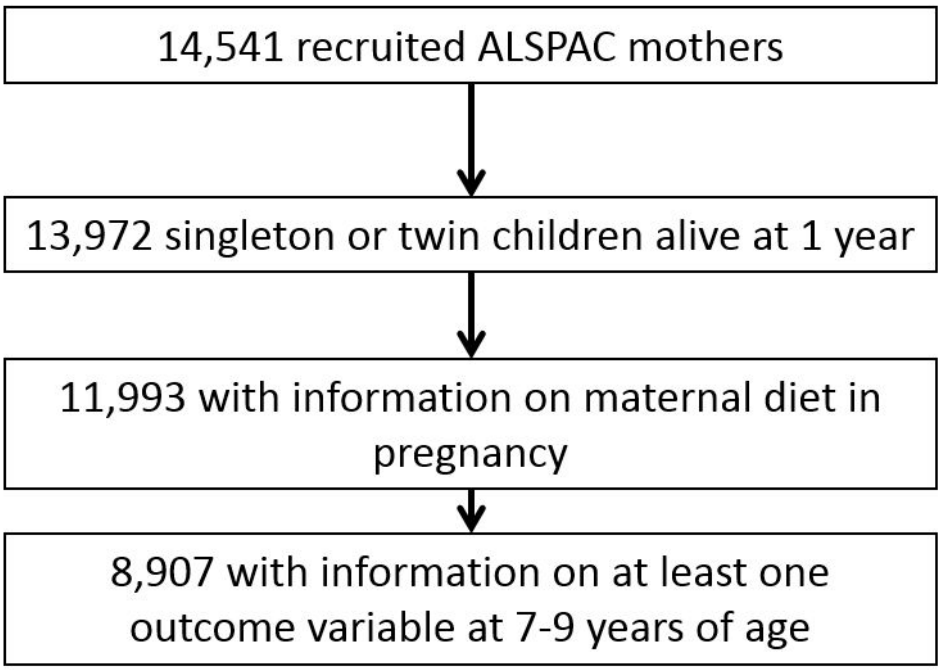
[a] Controlling for energy intake

[b] Controlling for energy intake, smoking, infections, supplements, antibiotics and paracetamol use during pregnancy; maternal educational level, housing tenure, financial difficulties, ethnicity, age, parity, maternal history of atopic diseases, anxiety score; sex of child, season of birth, multiple pregnancy, breastfeeding duration

Online Figure S1. Directed acyclic graph showing potential confounders and mediators of the associations between maternal Mediterranean diet score in pregnancy and offspring respiratory and atopic outcomes



Online Figure S2. Participant flow



STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.